REMARKS

Claims 1-5, 8-9, and 35-42 are presently pending in the application (claims 6-7 and 10-34 having been canceled by the present amendment and claims 35-42 having been added). Claims 1-3, 5, and 8 have been amended. Support for the amendment of claim 1 can be found throughout the specification (*see, e.g.*, the summary of the invention (particularly the paragraph beginning on page 3, line 25 and the paragraph at lines 3-26 of page 5) and Figures 9A-9C; *see also* Table 1 and page 20, lines 12-21). Claims 2 and 3 have been amended to provide an accurate antecedent basis (in view of the amendment of claim 1). Claim 5 has been amended to recite both HO1 and A20, genes whose use is described numerous times throughout the specification. Claim 8 has been amended so that it no longer depends from claim 6, which was canceled. New claim 35 specifies that the transplant rejection is chronic transplant rejection; new claim 36 specifies that the "at least one gene is A20"; and new claim 37 specifies that the method can be carried out by also determining the magnitude of expression of HO1. New claims 35-37 are supported throughout the specification and by original claims 10 and 11. New claim 38 specifies that the host is a human patient (see the specification at, for example, page 4, lines 14-16). New claim 39 specifies that the transplanted organ is a kidney (see the specification at, for example, page 4, line 16 *et seq.*). New claim 40 specifies that the post-transplant sample is obtained during the non-rejection period (see the first paragraph at page 6). New claim 41 specifies that the constitutively expressed gene is GADPH, and new claim 42 specifies that it is cyclophilin B or actin (see the specification at page 5 and Figures 9A-9C). No new matter has been added.

35 U.S.C. § 103

Claims 1-6 and 8-9 were rejected as being obvious in view of Soares *et al.* (*Nature Med.* 4:1073-1077, 1998; herein, "Soares"). For easy reference and completeness, the Examiner's remarks regarding Soares are reproduced on the following page in their entirety (they appear in the Office action at page 3).

Soares et al. disclose that the expression of the heme oxygenase-1 (HO-1) is functionally associated with xenograft survival and that rapid expression of HO-1 in cardiac xenografts can be essential to ensure long-term xenograft survival (See pg. 1073, the Abstract). The gene expression of HO-1 is also determined by immunocytochemistry and by reverse transcriptase (See pg. 1073, column 1, first paragraph). Expression of HO-1 was also detected in xenograft undergoing rejection (See pg. 1073, column 1, first paragraph) [as noted below, Applicants can see no reference to expression of HO-1 in rejection at this passage]. Soares et al. further address that expression of HO-1 by xenograft endothelial cells as in hearts from HO-1 $^{+/+}$ mice counteracts that xenograft rejection (See pg. 1076, second paragraph).

One of ordinary skill in the art at the time of the instant invention would have been motivated to evaluate acute transplant rejection in a host by determining the expression of the cytoprotective gene cluster with comparing the baseline of the gene expression of the protective gene and detecting the upregulation of the protective gene because of the study of expression of HO-1 in cardiac xenografts as disclosed by Soares et al., and the detection of the expression of HO-1 in xenograft undergoing rejection (See pg. 1073, column 1, first paragraph). It would have been prima facie obvious to carry out the method as claimed.

This ground for rejection should be withdrawn in view of the present amendment and the remarks that follow.

Soares does not satisfy the basic requirements of a *prima facie* case of obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. And third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Moreover, the teaching or suggestion to make the claimed combination *and* the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. MPEP at 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Soares cannot meet *any* of these three requirements. For example, Soares does not teach the method of claim 1. Soares was investigating the cellular mechanisms that underlie transplant rejection. He asked a particular mechanistic question: is HO-1 expression functionally associated

with xenograft survival (see page 1073, column 2)? To answer that question, Soares transplanted wild type hearts (which are HO-1 $^{+/+}$) and non-wild type hearts (HO-1 $^{+/-}$ and HO-1 $^{-/-}$) from mice into rats (see page 1073, column 2). The wild type hearts survived much longer than the non-wild type hearts. This result led Soares to conclude that "rapid expression of HO-1 in cardiac xenografts can be essential to ensure long-term xenograft survival" (Abstract). While the study suggested that HO-1 might have a role (even an important role) in transplant success, nothing in Soares' publication suggests that one should examine the expression of HO-1 (or any other gene in the cytoprotective gene cluster) in order to monitor the status of a transplanted organ. Soares' does not teach the use of expression data to predict the likelihood of graft rejection. Soares does not suggest all the limitations of Applicants' claim 1.

With respect to motivation, the Examiner states simply that "[o]ne of ordinary skill in the art ... would have been motivated to evaluate acute transplant rejection in a host" (Office action at page 3). But that conclusion cannot be fairly made on the basis of Soares alone. As Soares makes no suggestion that HO-1 relative expression should be used to monitor a transplanted organ, the Examiner's conclusion requires hindsight reconstruction. It comes only with Applicant's invention in view. Similarly, nothing in Soares provides the requisite expectation for success.

> Soares teaches away from Applicants' claimed method because Soares' primary finding is that HO-1 is *expressed in grafts that* ***survive*** (according to Applicants' method, HO-1 is *expressed in grafts undergoing acute* ***rejection***).

Even if there were a *prima facie* case of obviousness, it would be rebutted by the teaching away in Soares. Soares emphasizes a correlation between HO-1 expression and graft survival (for the reasons stated above, this does not mean Soares can meet the legal standard for obviousness). In addition to the conclusion stated in the Abstract, Soares teaches that:

> All *hearts from HO-1* $^{+/+}$ *mice* (n = 23), regardless of strain background *survived* long-term (more than 60 days (page 1073, column 2; emphasis added);
>
> *Overexpression of* either *HO-1* or A20 *protected* 2F-2B endothelial cells from apoptosis (page 1074, column 2; emphasis added);

And

> The rejection of HO-1 $^{-/-}$ hearts 3-5 days after transplant ... would indicate that early *expression of HO-1 is necessary to allow survival* of HO-1 $^{+/+}$ hearts (page 1074, column 2; emphasis added).

Thus, if one of ordinary skill in the art thought anything about modifying Soares' teaching to arrive at the predictive method Applicants now claim, Soares' data would lead one to a method in which expression or overexpression of HO-1 would predict *survival*. To the contrary, Applicants' found that expression or overexpression of HO-1 predicted acute graft *rejection*. Soares teaches away from the method now claimed.

Claims 10-11 were also rejected as being obvious (Office action at page 4). The Examiner found these claims unpatentable over Bach *et al.* (*Nature Med.* 3:106-204, 1997; herein, "Bach"). Claim 7 was rejected as being obvious over Soares in view of Bach (Office action at page 4).

Claims 7, 10, and 11 have been canceled, and Applicants respectfully note that application of these rejections to any of the claims now pending would be improper. Any rejection that relies on Soares would be improper for the reasons stated above. Any rejection that relies on Bach would be improper for similar reasons. Bach does not teach a method of monitor a transplant or of predicting graft rejection. Like Soares, Bach's finding is that HO-1 and A20 are *protective*. Thus, even if one of ordinary skill in the art might think to modify Bach's method, Bach's data would lead to a method in which expression or overexpression of HO-1 and A20 would be used to predict graft survival. In distinct contrast, Applicants discovered, and they now claim, a method of monitoring a transplant "wherein upregulation" of a cytoprotective gene "indicates that the host is likely to experience acute transplant *rejection*" (emphasis added). The prior art teaches away from Applicants' method.